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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/420,692	10/19/1999	JEFFREY M. BESTERMAN	106.101.197	3139

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EXAMINER	
ZARA, JANE J	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 08/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/420,692	BESTERMAN ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3-3-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 5-17-04.

Claims 1-3, 6 and 13 are pending in the instant application.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-3 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons of record set forth in the Office action mailed 2-13-04.

Applicant's arguments filed 5-17-04 have been fully considered but they are not persuasive. Applicants argue that adequate written description has been provided for the broad genus comprising *protein effectors of human DNA methyltransferase-1* because Example 6 and figures 19, 20A and B illustrate a synergistic effect using a combination of antisense to inhibit the expression of human DNA methyltransferase-1 and the protein inhibitor 5-aza-dC to inhibit DNA methyltransferase-1 activity.

Applicants argue further that various examples of protein effects are provided in USPN 6,268,137, including 5-aza-dC, 5-fluoro-2'-deoxycytidine, 5-aza-riboC, 5,6-dihydro-5-azacytidine, which adequately describe this broad genus. Applicants are correct that the instant disclosure (and the declarations filed 1-15-03) demonstrate a synergisitic reduction in human non-small cell lung, human colon and human bladder tumor cell growth in vitro following administration of antisense (MG88 or MG98) and 5-aza-dC; a synergistic increase in expression of $p24^{WAF1}$ and p16 proteins in human bladder tumor cells in vitro following administration of antisense (MG88 or MG98) and 5-aza-dC; a synergistic reduction in human colon and human bladder tumor cell growth in vivo in nude mice following intravenous administration of antisense (MG88 or MG98) and 5-aza-dC; and a reduction in tumor growth and an inhibition of expression of human DNA methyltransferase-1 in humans following intravenous administration of antisense MG98.

Contrary to Applicants' assertions, however, 5-aza-dC is not representative of the broad genus comprising protein effectors of DNA methyltransferase-1. The genus encompasses *any effector* of DNA methyltransferase (DNA MTase) protein function, including competitive, non-competitive and uncompetitive inhibitors (e.g. including allosteric effectors), and including proteins, peptides, inorganic and small organic molecule effectors, all of which operate via various and different mechanisms to inhibit protein function. The U.S. patent 6,268,137 cited by Applicants as support for providing adequate written description for the broad genus claimed concerns a particular type of DNA MTase inhibitor consisting of phosphorothioated IG, UG, 5-bromocytosineG, 5-fluorocytosineG, abasicG or CG dinucleotides in a hairpin structure. The common

mechanism for this class of inhibitors is to "bind the DNA MTase enzyme avidly in a noncovalent manner and inhibit DNA MTase in an S-adenosylmethionine-independent manner" (see col. 2-3 of USPN 6,268,137).

The genus claimed, however, is not limited to this class of protein effectors. It is much broader and no common structural attributes identify its members. A significant number of structural differences between members of the genus are permitted. Concise structural features that could distinguish structures or compounds within the genus from others are missing from the claims and the disclosure. Therefore, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus comprising protein effectors of DNA methyltransferase-1, and further whereby a synergistic effect is provided for treatment for any disease responsive to inhibition of human DNA methyltransferase-1 expression or activity.

Claims 1-3, 6 and 13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting the expression of human DNA methyltransferase-1 in vitro and in vivo comprising the systemic administration of antisense MG88 and MG98, and being enabling for a method for inhibiting tumor growth in vitro and in vivo comprising the systemic administration of antisense MG88 and MG98, and enabling for the synergisitic reduction in human non-small cell lung, human colon and human bladder tumor cell growth in vitro following administration of antisense (MG88 or MG98) and 5-aza-dC, for a synergistic increase in expression of $p24^{WAF1}$ and p16 proteins in human bladder tumor cells in vitro following administration of antisense (MG88 or MG98) and 5-aza-dC, and for a synergistic

reduction in human colon and human bladder tumor cell growth in vivo following intravenous administration of antisense (MG88 or MG98) and 5-aza-dC, does not reasonably provide enablement for methods for inhibiting tumor growth or treating a disease comprising the administration of any antisense oligonucleotide that specifically targets human DNA methyltransferase-1, or synergistic treatment or effects comprising the administration of any antisense that specifically targets human DNA methyltransferase-1 and any protein effector of human DNA methyltransferase-1 for the reasons of record set forth in the Office action mailed 2-13-04.

Applicant's arguments filed 5-17-04 have been fully considered but they are not persuasive. Applicants argue that the full scope claimed is enabling because undue experimentation is not required beyond the instant disclosure combined with the experimental results provided in the declaration of Dr. Szyf (filed 1-15-03). Applicants also argue that the full scope is enabled because Example 6 and figures 19, 20A and B of the instant disclosure illustrate a synergistic effect using a combination of antisense to inhibit the expression of human DNA methyltransferase-1 and the protein inhibitor 5-aza-dC to inhibit DNA methyltransferase-1 activity. Applicants are correct that the instant disclosure and the declarations filed 1-15-03 together demonstrate a synergisitic reduction in human non-small cell lung, human colon and human bladder tumor cell growth in vitro following administration of antisense (MG88 or MG98) and 5-aza-dC; a synergistic increase in expression of $p24^{WAF1}$ and p16 proteins in human bladder tumor cells in vitro following administration of antisense (MG88 or MG98) and 5-aza-dC; and a synergistic reduction in human colon and human bladder tumor cell growth in vivo in

nude mice following intravenous administration of antisense (MG88 or MG98) and 5-aza-dC; and a reduction in tumor growth and an inhibition of expression of human DNA methyltransferase in humans following intravenous administration of antisense MG98. But these demonstrations of target gene inhibition and synergy are not enabling for the broader scope drawn to treatment methods and synergistic effects comprising the administration of any antisense specifically targeting DNA methyltransferase-1, nor are they enabling for the broad genus comprising any protein effector of human DNA methyltransferase-1. The results of in vivo target gene inhibition obtained for a particular antisense cannot be extrapolated to another antisense, nor can the in vitro results of an antisense be extrapolated to in vivo effects. The synergy obtained in treatment effects using one protein effector, 5-aza-dC, cannot be extrapolated to that using any protein effector (e.g. using a different and distinct mechanism of inhibition). It would require undue experimentation beyond that taught in the instant disclosure to demonstrate synergy in treatment effects provided comprising the administration of other protein effectors, and it would require undue experimentation to demonstrate in vivo targeting, inhibition and treatment effects provided for other antisense that target DNA methyltransferase-1.

Claims 1-3, 6 and 13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting for the reasons of record set forth in the Office action mailed 2-13-04.

No arguments addressing this rejection have been made in the reply filed 5-17-04.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ
8-18-04

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
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